REMARKS

I. STATUS OF THE CLAIMS

Claims 1 to 7 and 14-15 have been considered by the Examiner, while claims 8 to 10 and 12 have been withdrawn. Claims 11 and 13 have been cancelled.

Claim 1 has been amended. Support for the amendment can be found throughout the application, specifically in the Examples, ¶ [0059], original claims 3-4,

No new matter has been added.

II. EXAMINER INTERVIEW SUMMARY

Applicants thank the Examiner for the interview of January 26, 2012. Applicants discussed the Examiner's interpretation of claim 1 as a product-by-process claim and sought clarification for that interpretation. The Examiner indicated that if claim 1 was amended to recite expression of the E1A and E1B 55K genes, as noted in the Office Action Mailed September 27, 2011 (hereafter "Action")(p. 4, ¶ 3), claim 1 would no longer be interpreted as a product-by-process claim.

III. RESPONSE TO CLAIM OBJECTIONS

Claim 1 is objected to by the Examiner. The Examiner suggests that the term "an adenovirus" should be inserted in front of the term "early region 1A (E1A) gene" (see Action, p.3-4).

Without agreeing with the need for amendment, claim 1 has been amended as suggested to recite "a mastadenovirus" before the term "early region 1A (E1A) gene." The source of the E1A gene as recited by the claim is from the genus mastadenovirus. Specific support for "mastadenovirus E1A" genes can be found at ¶[0052], [0062] and original claims 4-5.

Applicants respectfully request that the claim objection be withdrawn.

IV. RESPONSE TO REJECTIONS UNDER 35 USC § 102

The Action rejects claim 1 under 35 U.S.C. § 102(b) as being anticipated by Kim *et al.* (1995, Oncogene 20: 2671-2682)(hereafter "Kim, *et al.*"). The Examiner interprets claim 1 as a product-by-process claim. Therefore, the Action asserts that "an immortalized avian cell line may not even require the recited genes" and "any avian immortalized cell line reads on the claimed invention." (Action, p.4, ¶ 3). Applicants respectfully disagree with this interpretation and the rejection under 35 U.S.C. § 102(b).

As an initial matter, while Applicants disagree with the need for amendment, Applicants have amended claim 1 to recite "*wherein said first and second viral genes are expressed in said cell line*." As discussed during the Examiner Interview, amended claim 1 cannot be considered a product-by-process claim, for the expression of both the first and second (E1A and E1B 55K) genes are required elements of this claim, as evidenced by the "comprising" language. Thus, the immortal avian cell line of amended claim 1 necessarily requires the E1A and E1B 55K genes. Amended claim 1 also requires the expression of said genes, which produces to the immortalization of said avian cell. (See Example 3).

For further clarification, claim 1 has also been amended to recite "immortal" rather than "immortalized." Amended claim 1 recites no "process" and no "immortalizing means." (See Action, p.5). Therefore, Applicants assert that it is clear that claim 1 is not a product-by-process claim, since it requires the E1A and E1B 55K genes and their expression.

The E1A and E1B 55K genes and their expression are claim elements which are not described in Kim, *et al.* Kim, *et al.* discloses a cell line which is "non-virally and non-chemically immortalized" (see Kim, *et al.*, Abstract). Kim, *et al.* does not provide either (i) a first viral gene which is a Mastadenovirus early region 1A (E1A) gene; or (ii) a second viral gene which codes for a Mastadenovirus early region 1B 55K (E1B 55K) protein; or (iii) the expression of said first

and second viral genes in the avian cell line. Kim, *et al.*, describes no specific viral genes, and therefore cannot meet any of the claim elements (i)-(iii) as listed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See* M.P.E.P. 2131. Kim, *et al.* does not disclose all of the elements of claim 1, and therefore cannot anticipate claim 1 under 35 U.S.C. § 102(b). Applicants respectfully request reconsideration of this rejection.

V. RESPONSE TO REJECTIONS UNDER 35 USC § 103

Claims 1-6 and claims 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouquet *et al.*, (U.S. Patent 6,255,108)(hereinafter "Bouquet *et al.*") in view of Kim *et al.*, and further in view of Pau *et al.*, (U.S. Patent 7,192,759)(hereinafter "Pau *et al.*"), as evidenced by Bagchi *et al.*, (Cell 1991, pp. 1063-1072)(hereinafter "Bagchi *et al.*") and Renee *et al.*, (1992, Nature pp. 82-85)(hereinafter "Renee *et al.*"). Applicants respectfully disagree with this rejection. While acknowledging that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references, Applicants address the Action's arguments in turn.(See Action, p.10-11, citing *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Action asserts that the activity of the SV40 T antigen, as shown in Bouquet *et al.* and Kim *et al.*, can be used to predict the activity of E1A and E1B. (See Action, p. 10). The Action concludes from the teachings of Bouquet *et al.* that if transformation of avian cells with viral oncoprotein SV40 virus generates immortalized cells, transformation of avian cells with a gene encoding *any viral protein*, e.g. E1A and E1B, should be reasonably expected to immortalize avian cells. (See Action, p. 10, ¶ 2). Applicants respectfully disagree. One of ordinary skill in the art could not and would not predict the activity of E1A or E1B viral proteins based on SV40 activity, since these viral proteins are so different. This position is supported by the attached "Declaration Under 37 C.F.R. § 1.132" by Dr. Ingo Jordan (hereafter "Jordan Dec. No. 2").

As an initial matter, the Action's statement that "if transformation of avian cells with viral oncoprotein SV40 virus early region generates immortalized cells, transformation of avian cells

with a gene encoding any viral protein should be reasonably expected to immortalize[] avian cells" is incorrect. (See Action, p. 10, ¶ 2). Many viral genes are not suited for the immortalization of cells due to safety reasons. For this reason, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require that the immortalized producer cell for the preparation of vaccines is well characterized and does not contain aggressive oncogenes, such as SV40 large T antigen. (See Exhibit A, at p.4-5). Immortalizing factors from SV40 or HPV-16 are known to efficiently transform cells. However, experts in the virology field consider them as being too dangerous for use in most applications, particularly vaccine preparation. (See Jordan Dec. No. 2, ¶ 7).

For example, the SV40 large T antigen is has long been recognized among skilled persons to be a tumor inducer. *See* e.g. May *et al.* "SV40-related T-antigen expression in human Meningiomas with normal and G-22-monosomic karyotype", 43 J. Gen. Virol. (1979), p. 697 to 700. More recently, data from several laboratories collected during the last decade indicates that SV40 has a strong carcinogenetic effect causing mesothelioma in rodents and malignant transformation of human mesothelial cells. *See* e.g. Yang H. *et al.* "Mesothelioma Epidemiology, Carcinogenesis and Pathogenesis", Curr. Treat. Options Oncology, 2008, June, 9 (2-3), pages 147-157.

The behavior of adenoviral proteins E1A or E1B in avian cells cannot be predicted by unrelated SV40 large T-antigen studies. Since the E1A and E1B viral proteins are significantly different than the SV40 large T-antigen, one of ordinary skill in the art would not consider predicting the properties of other viral proteins bases on SV40 studies. For example, while SV40 has been shown in the literature to cause spontaneous transformation events leading to tumors (see references cited above and Jordan Dec. No. 2, ¶ 7), none of these events were observed in the claimed avian cell line (see Application, Example 3, [0137]). Both Kim *et al.*, and Bouquet *et al.* are completely silent as to the activity of viral genes E1A and E1B and their expression. Since the E1A and E1B viral proteins are significantly different than the SV40 large T-antigen, one of ordinary skill in the art would not consider the SV40 findings of Kim *et al.*, and Bouquet *et al.* to provide any teaching, suggestion, or motivation as to any properties of E1A and E1B.

Pau *et al.* is directed to an immortalized human embryonic retina cell line comprising human adenovirus E1A and E1B coding sequences (e.g. PER.C6). Despite the presence of p53

and E2F-1 homologs in both cell types, one of ordinary skill in the art could not predict E1A and E1B activity on p53 and E2F-1 in avian cells merely from their activity in human cells. (See Jordan Dec. No. 2, ¶ 9).

The Action asserts that Kim *et al.*, teaches that functional inactivation of the p53 and Rb regulatory pathways are known to be common events for cellular immortalization. (Action, p.7). However, the mechanisms of these pathways are not necessarily conserved between human and avian cells. As further described in Kim *et al.*, the mechanisms for deregulating p53 and E2F-1 as well as telomeric maintenance found in the immortal chicken embryo fibroblast (CEF) cells are *different from previously known genetic alterations in humans* (see p. 2677, left column, second paragraph). Without knowledge that these particular pathways and/or mechanisms are conserved between human and avian cells, one of ordinary skill in the art would not be able to predict the activity of interacting proteins, such as E1A or E1B, across species.

Kim *et al.* indicates that the p53 and E2F-1 regulatory mechanisms are different between human and avian cells, suggesting that E1A or E1B interaction studies in one cell species could not be used to predict activity in the other cell species. The difference in p53 regulation between human and avian cells can further be explained by the extremely low homology between chicken and human p53, as discussed in the previous Office Action Response filed 9/7/2011.

Finally, mastadenoviruses and fowl adenoviruses do not conserve the sequence of regulatory proteins. (See Jordan Dec. No. 2, ¶ 9). This is not common, for generally viruses within a family tend to conserve the sequence of regulatory proteins. According to the literature, no mastadenovirus homologues of E1A and E1B can be found in fowl. (See Jordan Dec. No. 2, ¶ 9).

One of ordinary skill in the art would not predict E1A or E1B activity across species. In view of the above differences in key regulatory mechanisms between humans and avian cells, as well as the divergence between mastadenoviruses and fowl adenoviruses, it is clear that the biochemical processes in birds are very different to those in mammals.

Due to this uncertainty in the virology field, it was an unexpected result that complete immortalization of avian cells could be achieved via expression of only the E1A and E1B 55K

genes from mastadenoviruses. (Jordan Dec. No. 2, ¶ 4-6). The inventors surprisingly found that the expression of two defined viral genes, namely (i) a first viral gene which is a Mastadenovirus early region 1A (E1A) gene, and (ii) a second viral gene which codes for a Mastadenovirus early region 1B 55K (E1B 55K) protein, in the avian cell line was sufficient for the immortalization of said cell line.

The teachings of Guilhot *et al.*, confirm the unexpected nature of this result. Guilhot *et al.*, shows that the 12S E1A protein is not sufficient to immortalize avian cells, for the process failed when the gene was introduced by transfection of naked DNA instead of retrovirus infection. (See ¶ [0036]). Only after exposing the cells to a growth crisis period was Guilhot *et al.*, able to immortalize cells by expressing the 12S E1A protein using retrovirus. (Jordan Dec. No. 2, ¶ 8). Indeed, Guilhot *et al.* stated that expressing early viral genes "should be important for immortalization of avian cells but might not be sufficient." (Guilhot *et al.*, p.623, left column, ¶ 3). The avian cell line generated in the claimed invention runs contrary to Guilhot *et al.*, and shows the surprising result that the early viral genes indeed are sufficient to achieve immortalization of avian cells. (Jordan Dec. No. 2, ¶ 6).

Finally, the new avian cell line exhibited many superior properties to other immortalized cell lines. Most importantly, while other viral genes have been shown to cause tumors when used for immortalizing cells (e.g. SV40 T-antigen), no spontaneous transformation events were observed in the claimed avian cell line (see Application, Example 3, at ¶ [0137]). Also unexpected is the claimed cell line's lack of contaminants, which are often seen in cells immortalized using viral genes, thus limiting their use. (See Jordan Dec. No. 2, ¶ 5; Application at ¶ [0031]). Accordingly and unexpectedly, this cell line is safe and ideally suited for the production of vaccines and gene therapy vectors. (Jordan Dec. No. 2, ¶ 6).

One of ordinary skill in the art cannot predict the activity of E1A or E1B proteins in avian cells by comparing the activity of different viral proteins (e.g. SV40) or activity in human cells with well-known differences in the regulatory mechanisms and amino acid sequences if p53 and E2F-1. Therefore, none of the cited references provide sufficient teaching to render obvious the avian cell line of the claimed invention. It was unexpected that the expression of E1A and E1B genes would be sufficient to immortalize avian cells, such that the resulting cell line would

possess many favorable properties, including the safety profile. Since the claimed cell line is non-obvious, Applicants respectfully request reconsideration of this rejection.

VI. CONCLUSION

Applicants respectfully request consideration of the remarks herein. If the Examiner has any questions regarding this response, she is invited to call the undersigned attorney.

General Authorization Regarding Fees

While Applicants do not believe there are any fees due at this time, the Office is authorized to deduct any fee associated with the filing of this paper, or for any other matter related to the application, or credit any overpayment, to Deposit Account No. 13-2490.

Respectfully submitted,

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